2

Methods and Approaches Used

OVERVIEW

Carbohydrate, fat, and protein all have two major functions as classes of nutrients: they are required for many normal biological functions, and they serve as energy sources for body fuel. Physical activity can modulate the amount of energy required by the body. Specific subcomponents, such as some amino acids and fatty acids, are required for normal growth and development. Other subcomponents, such as fiber, play a role in decreasing risk of chronic disease.

Carbohydrate and fat are the primary fuel sources. For this purpose they can be largely utilized interchangeably. On the other hand, many metabolic processes favor one source over another. For example, under normal circumstances the brain functions almost exclusively on glucose (Dienel and Hertz, 2001). Conversely, membranes are composed of specific lipids. To a large extent, the body can synthesize de novo the lipids and carbohydrates it needs for these specialized functions. An exception is the requirement for small amounts of carbohydrate and *n*-6 and *n*-3 polyunsaturated fatty acids. Otherwise, there are no specific "dietary requirements"[1] for fat or carbohydrate for specific functions. Of course, some mixture of fat and carbohydrate is required as a source of fuel to meet the energy requirements of the body.

In order to apply the Dietary Reference Intake (DRI) process and approach to energy-yielding macronutrients, it was necessary to separate

[1]A requirement is defined as the lowest continuing intake level of a nutrient that, for a specific indicator of adequacy, will maintain a defined level of nutriture in an individual.

out the metabolic requirements for specific nutrients for which Estimated Average Requirements (EARs) or Adequate Intakes (AIs) have been derived. It was also necessary to provide quantitative guidance on proportions of specific sources of required energy based on evidence of decreased risk of disease (which, in most cases, is chronic disease).

Thus, a fundamental question to be addressed when reviewing the role of these nutrients in health is, What is the most desirable mix of energy sources that maximizes both health and longevity? Because individuals can live apparently healthy lives for long periods with a wide range of intakes of specific energy nutrients, it is not surprising that this optimal mix of such sources may be difficult to define. There are no clinical trials that compare various energy sources with longevity in humans. For this reason, recommendations about the desirable composition of energy sources must be based on either short-term trials that address specific health or disease endpoints, or surrogate markers (biomarkers) that correlate well with these endpoints. A large number of research studies have been carried out to examine the effects of the composition of energy sources on surrogate markers, and these have provided a basis for making recommendations.

Because diets with specific ratios of carbohydrate to fat, or specific ratios of subcomponents of each, have associations with the risk of various clinical endpoints (e.g., coronary heart disease, diabetes), Acceptable Macronutrient Distribution Ranges (AMDRs) have been proposed that consider these endpoints, as well as the need to consume diets that meet recommended intakes for micronutrients and essential fatty acids. These ranges are given as percentages of total energy intake. For any given diet consumed by an individual, the sum of the contribution to energy intake as a percentage of total intake for carbohydrate, fat, protein, and alcohol must equal 100 percent. The acceptable range of macronutrient intake is a range of intakes for a particular nutrient or class of nutrients that will confer decreased risk of disease and provide the most desirable long-term health benefits to apparently healthy individuals.

TYPES OF DATA USED

A number of disciplines have made key contributions to the evidence linking energy-yielding nutrients to outcomes that may relate to human health. Basic biological research, often involving animal models, provides critical information on mechanisms that may link nutrient consumption to beneficial or adverse health outcomes. While results from animal experiments are generally not used when establishing Dietary Reference Intakes (DRIs), selected animal studies are considered in the absence of human data.

Observational studies in humans include single-case and case-series reports and cross-sectional, cohort, and case-control studies. Experimental studies include randomized and nonrandomized therapeutic or prevention trials and controlled dose–response, balance, turnover, factorial, and depletion–repletion physiological studies. Clinical and epidemiological observational studies play a valuable role in generating hypotheses concerning the health risks and benefits of nutrient intake patterns. Randomized clinical trials in population groups of interest have the potential to provide definitive comparisons between selected nutrient intake patterns and subsequent health-related outcomes. Note, however, that randomized trials attempting to relate diet to disease states also have important limitations, which are elaborated in the discussion below.

Animal Models

Basic research using experimental animals affords considerable advantage in terms of control of nutrient exposures, environmental factors, and even genetics. In contrast, the relevance to free-living humans is often unclear. In addition, dose levels and routes of administration that are practical in animal experiments may differ greatly from those relevant to humans. Nevertheless, due to the opportunity to elaborate specific mechanisms of action, evidence from animal feeding experiments regarding protein, fat, and carbohydrate were included in the evidence reviewed when developing the decisions concerning the ability to specify the DRIs for these nutrients.

Human Feeding Studies

Controlled feeding studies, usually in a confined setting such as a metabolic unit, can yield valuable information on the relationship between nutrient consumption and health-related biomarkers. Much of the understanding of human nutrient requirements to prevent deficiencies is based on studies of this type. Studies in which the subjects are confined allow for close control of intake and activities and complete collection of nutrient or metabolite losses through urine and feces. Recurring sampling of biological materials, such as blood and skin sloughing, is also possible in this type of setting.

Nutrient balance studies measure nutrient status in relation to intake at various levels. Depletion–repletion studies, by contrast, measure nutrient status while subjects are maintained on diets containing marginally low or deficient levels of a nutrient; the deficit is then corrected with measured amounts of the nutrient under study over a period of time. However, these two types of studies have several limitations. Typically, due to

resource constraints, they are limited in time to a few days or weeks, so longer-term outcomes cannot be measured with the same level of accuracy. In addition, since subjects are often confined, findings cannot necessarily be generalized to free-living individuals. Finally, the time and expense involved in such studies usually limit the number of subjects and the number of doses or intake levels that can be tested.

In spite of these limitations, feeding studies have played an important role in understanding nutrient needs and metabolism. Such data were considered in the DRI process and were given particular attention in the absence of reliable data to directly relate nutrient intake to disease risk in free-living individuals.

Observational Studies

In comparison to human feeding studies, observational epidemiological studies are frequently of direct relevance to free-living humans, but they lack the controlled setting. Hence, they are useful in establishing evidence of an association between the consumption of a nutrient and disease risk, but are limited in their ability to ascribe a causal relationship. A judgment of causality may be supported by a consistency of association among studies in diverse populations under various conditions, and it may be strengthened by the use of laboratory-based tools to measure exposures and confounding factors, rather than other means of data collection such as personal interviews.

In recent years, rapid advances in laboratory technology have made possible the increased use of biomarkers of exposure, susceptibility, and disease outcome in molecular epidemiological research. For example, one area of great potential in advancing current knowledge of the effects of diet on health is the study of genetic markers of disease susceptibility (especially polymorphisms in genes that encode metabolizing enzymes) in relation to dietary exposures. This development is expected to provide more accurate assessments of the risk associated with different levels of intake of nutrients and other food constituents.

While analytic epidemiological studies (studies that relate exposure to disease outcomes in individuals) have provided convincing evidence of an associative relationship between selected nondietary exposures and disease risk, there are a number of other factors that limit study reliability in research relating nutrient intakes to disease risk (Sempos et al., 1999). First, the variation in nutrient intake may be rather limited in the population selected for study. This feature alone may yield modest relative risk across intake categories in the population, even if the nutrient is an important factor in explaining large disease-rate variations among populations.

A second factor, one that gives rise to particular concerns about con-

founding, is the human diet's complex mixture of foods and nutrients that include many substances that may be highly correlated. Third, many cohort and case-control studies have relied on self-reports of diet, typically from food records, 24-hour recalls, or diet history questionnaires. Repeated application of such instruments to the same individuals shows considerable variation in nutrient consumption estimates from one time period to another with correlations often in the 0.3 to 0.8 range (Willett et al., 1985).

In addition, there may be systematic bias in nutrient consumption estimates from self-reports, as the reporting of food intakes and portion sizes may depend on individual characteristics such as body mass, ethnicity, and age. For example, some have demonstrated more pronounced and substantial underreporting of total energy consumption among obese persons than among lean persons (Heitmann and Lissner, 1995; Schoeller et al., 1990). Such systematic bias, in conjunction with random measurement error and limited intake range, has the potential to greatly impact analytical epidemiological studies based on self-reported dietary habits. Cohort studies using objective (biomarker) measures of nutrient intake may have an important advantage in the avoidance of systematic bias, though important sources of bias (e.g., confounding) may remain.

Finally, there can be the problem of multicollinearity, in which two independent variables are related to each other, resulting in a low p value for an association with a dependent variable, when in fact each of the independent variables have no relationship to the dependent variable (Sempos et al., 1999).

Randomized Clinical Trials

By randomly allocating subjects to the nutrient exposure level of interest, clinical trials eliminate the confounding that may be introduced in observational studies by self-selection. The unique strength of randomized trials is that, if the sample is large enough, the study groups will be similar not only with respect to those confounding variables known to the investigators, but also to other unknown factors that might be related to risk of the disease. Thus, randomized trials achieve a degree of control of confounding that is simply not possible with any observational design strategy, and thus they allow for the testing of small effects that are beyond the ability of observational studies to detect reliably.

Although randomized controlled trials represent the accepted standard for studies of nutrient consumption in relation to human health, they too possess important limitations. Specifically, individuals agreeing to be randomized may be a select subset of the population of interest, thus limiting the generalization of trial results. For practical reasons, only a small number of nutrients or nutrient combinations at a single intake level

are generally studied in a randomized trial (although a few intervention trials to compare specific dietary patterns have been initiated in recent years). In addition, the follow-up period will typically be short relative to the preceding time period of nutrient consumption; the chronicity of intake may be relevant to the health outcomes under study, particularly if chronic disease endpoints are sought. Also, dietary intervention or supplementation trials tend to be costly and logistically difficult, and the maintenance of intervention adherence can be a particular challenge.

Many complexities arise in conducting studies among free-living human populations. The totality of the evidence from observational and intervention studies, appropriately weighted and corroborated by an understanding of the underlying mechanisms of action, must form the basis for conclusions about causal relationships between particular exposures and disease outcomes.

Weighing the Evidence

As a principle, only studies published in peer-reviewed journals have been used in this report. However, raw data or studies published in other scientific journals or readily available reports were considered if they appeared to provide important information not documented elsewhere.

For estimating requirements for energy, doubly labeled water data was collected from various investigators and subject to statistical analysis (see Appendix I). For other nutrients, to the extent possible, original scientific studies have been used to derive the DRIs. On the basis of a thorough review of the scientific literature, clinical, functional, and biochemical indicators of nutritional adequacy and excess were identified for each nutrient.

The quality of the studies was considered in weighing the evidence. The characteristics examined included the study design and the representativeness of the study population; the validity, reliability, and precision of the methods used for measuring intake and indicators of adequacy or excess; the control of biases and confounding factors; and the power of the study to demonstrate a given difference or correlation. Publications solely expressing opinions were not used in setting DRIs. Each assessment acknowledged the inherent reliability of each type of study design as described above, and standard criteria concerning the strength and dose–response and temporal pattern of estimated nutrient–disease or adverse effect associations, the consistency of associations among studies of various types, and the specificity and biological plausibility of the suggested relationships were applied (Hill, 1971). For example, biological plausibility would not be sufficient in the presence of a weak association and lack of evidence that exposure preceded the effect.

Data were examined to determine whether similar estimates of the requirement resulted from the use of different indicators and different types of studies. For a single nutrient, the criterion or indicator of adequacy for setting the Estimated Average Requirement (EAR) may differ from one life stage group to another because the critical function, the risk of a disease, or its biomarker may be different. When very poor or no data were available for a given life stage group, extrapolation was made from the EAR, Adequate Intake (AI), or Tolerable Upper Intake Level (UL) set for another group; explicit and logical assumptions on relative requirements or potential risk of adverse effects were made. Because EARs can be used for multiple purposes, they were established whenever sufficient supporting data were available.

Data Limitations

Although the reference values are based on data, the data were often scanty or drawn from studies that had limitations in addressing the various questions that arose in reviewing the data. Therefore, many of the questions raised about the requirements for, and recommended intakes of, these nutrients cannot be answered fully because of inadequacies in the present database. Apart from studies of overt deficiency diseases, there is a dearth of studies that address specific effects of inadequate intakes on specific indicators of health status, and thus a research agenda is proposed (see Chapter 14). For many of these nutrients, estimated requirements are based on balance, biochemical indicators, and clinical deficiency data because there is little information relating health status indicators to functional sufficiency or insufficiency.

Thus, after careful review and analysis of the evidence, including examination of the extent of congruent findings, scientific judgment was used to determine the basis for establishing the values. The reasoning used in developing the values is described for each nutrient in Chapters 5 through 11.

METHODS TO DETERMINE THE ADEQUATE INTAKE FOR INFANTS

As for other nutrients in previous Dietary Reference Intake (DRI) reports, the Adequate Intake (AI) for young infants (ages 0 through 6 months) is generally estimated to be the average intake by full-term infants who are born to healthy, well-nourished mothers and who are exclusively fed human milk. The extent to which intake of a nutrient from human milk may exceed the actual requirements of infants is not known, and ethics of human experimentation preclude the testing of levels known to

be potentially inadequate. Using the infant exclusively fed human milk as a model is in keeping with the basis for earlier recommendations for intake (e.g., Health Canada, 1990; IOM, 1991). It also supports the recommendation that exclusive intake of human milk is the preferred method of feeding for normal, full-term infants for the first 4 to 6 months of life. This recommendation has been made by the Canadian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), the Institute of Medicine (IOM, 1991), and many other expert groups, even though most infants in the United States no longer receive human milk by the age of 6 months.

In general, this report does not cover possible variations in physiological need during the first month after birth or the variations in intake of nutrients from human milk that result from differences in milk volume and nutrient concentration during early lactation. In keeping with the decision made by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, specific DRIs to meet the needs of formula-fed infants have not been proposed in this report. The use of formula introduces a large number of complex issues, one of which is the bioavailability of different forms of the nutrient in different formula types. Where data are available regarding adjustments that should be made for various formulas, they are included in the "Special Considerations" sections of the nutrient chapters.

Ages 0 Through 6 Months

Except for energy, the AI for infants ages 0 through 6 months was based on: (1) the average concentration of the nutrient in human milk from mothers who had been lactating from 2 to 6 months (using consensus values from several reported studies, if possible), and (2) an average volume of milk intake of 0.78 L/d. This volume was reported from studies that used test weighing of full-term infants. In this procedure, the infant is weighed before and after each feeding (Allen et al., 1991; Hofvander et al., 1982; Michaelsen et al., 1994; Neville et al., 1988). Because there is variation in both the composition of milk and the volume consumed, the computed value represents the mean. It is assumed that infants will consume increased volumes of human milk during growth spurts to meet their needs for maintenance, as well as for growth.

Ages 7 Through 12 Months

There is evidence for different nutrient needs for energy, protein, and amino acids during the period of infant growth and gradual weaning to a

mixed diet of human milk and solid foods from ages 7 through 12 months. There is little evidence, however, of markedly different needs for carbohydrate, fat, and *n*-6 and *n*-3 polyunsaturated fatty acids.

In previous DRI reports, some Estimated Average Requirements (EARs) for this age group were determined by extrapolating down from the EAR for young adults by adjusting for metabolic or total body size and growth. The AI was extrapolated up for infants ages 0 through 6 months by using the same type of adjustment (IOM, 2000). However, for the energy-yielding nutrients, these methods were not appropriate because the amount of energy required per body weight is significantly lower during the second 6 months, due largely to the slower rate of weight gain/kg of body weight.

Instead, the basis of the AIs derived for this age category for carbohydrate, fat, *n*-6 and *n*-3 polyunsaturated fatty acids, and protein was the sum of: (1) the content of the nutrient provided by 0.6 L/d of human milk, which is the average volume of milk reported from studies of infants receiving human milk in this age category (Dewey et al., 1984; Heinig et al., 1993), and (2) the content of the nutrient provided by the usual intakes of complementary weaning foods consumed by infants in this age category. Such an approach is in keeping with the current recommendations of the Canadian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), and the Institute of Medicine (IOM, 1991) for continued feeding of infants with human milk through 9 to 12 months of age with appropriate introduction of solid foods. This method has also been used for some nutrients in previous DRI reports.

The amounts of fat and carbohydrate consumed from complementary foods were determined by using data from the Third National Health and Nutrition Examination Survey. One problem encountered in deriving intake data in infants was the lack of available data on total nutrient intake from a combination of human milk and solid foods in the second 6 months of life. Most intake survey data do not identify the milk source, but the published values indicate that cow milk and cow milk formula were most likely consumed. Thus, it is assumed in deriving the AIs for infants 7 through 12 months of age that complementary food intake is similar in both infants consuming human milk and formula-fed infants.

METHODS TO DETERMINE THE DIETARY REQUIREMENTS FOR CHILDREN AND ADULTS

Setting Estimated Average Requirements for Children and Adults

As described previously, various types of studies can be considered for estimating an average requirement. As discussed in Chapter 1, additional

analysis of the data (e.g., transformation of data when nutrient requirements are not normally distributed) may be required. For determining estimated energy requirements using a doubly labeled water database, equations using stepwise multiple linear regressions were generated to predict total energy expenditure based on age, gender, height, and weight.

Extrapolating Data from Adults to Children

When data are lacking to set an Estimated Average Requirement (EAR) or Adequate Intake (AI) for children and adolescents, the EAR or AI can be extrapolated down by scaling requirements to the 0.75 power of body mass (IOM, 2001), which adjusts for metabolic differences demonstrated to be related to body weight, as described by Kleiber (1947) and explored further by West and coworkers (1997). Other approaches include extrapolating down based on the reference body weights, which has been done in developing Tolerable Upper Intake Levels (ULs) for some nutrients (IOM, 1997). Neither of these approaches, however, was used for setting an EAR or AI for the macronutrients under review as adequate data were available to develop Dietary Reference Intakes (DRIs) directly for the younger age groups.

Setting the Recommended Dietary Allowance for Children and Adults

To account for variability in requirements because of growth rates and other factors, a 10 percent coefficient of variation (CV) for the requirement is assumed unless data are available to support another value, as described in Chapter 1. For carbohydrate, protein, and the indispensable amino acids where EARs have been established, the CV was determined to be greater than 10 percent.

Methods to Determine Increased Needs for Pregnancy

It is known that the placenta actively transports certain nutrients from the mother to the fetus against a concentration gradient (Hay, 1994). However, for many nutrients, experimental data that could be used to set an EAR or AI for pregnancy are lacking. In these cases, the potential for increased need for these nutrients during pregnancy is based on theoretical considerations, including obligatory fetal transfer, if data are available, and on increased maternal needs related to increases in energy or protein metabolism, as applicable. Thus, in some cases, the EAR can be determined by the additional weight gained during pregnancy. Carmichael and colleagues (1997) reported that the median weight gain of women who

had good pregnancy outcomes was approximately 16 kg. In six studies of U.S. women, no consistent relationship between maternal age and weight gain was observed (IOM, 1990). Therefore, as is the case for protein, 16 kg is added to the reference weight for nonpregnant adolescent girls and women for setting the EAR.

Methods to Determine Increased Needs for Lactation

For the nutrients under study, it is assumed that the total requirement of lactating women equals the requirement for the nonpregnant, nonlactating woman of similar age plus an increment to cover the amount needed for milk production. To allow for inefficiencies in use of certain nutrients, the increment may be greater than the amount of the nutrient contained in the milk produced. Details are provided in each nutrient chapter.

ESTIMATES OF NUTRIENT INTAKE

Reliable and valid methods of food composition analysis are crucial in determining the intake of a nutrient needed to meet a requirement. While data regarding total fat, cholesterol, protein, and amino acid content of various foods have been available for many years, data for individual fatty acids have only recently been available. For nutrients such as energy, fiber, and *trans* fatty acids, analytical methods to determine the content of the nutrient in food have serious limitations.

Methodological Considerations

The quality of nutrient intake data varies widely across studies. The most valid intake data are those collected from the metabolic study protocols in which all food is provided by the researchers, amounts consumed are measured accurately, and the nutrient composition of the food is determined by reliable and valid laboratory analyses. Such protocols are usually possible with only a few subjects. Thus, in many studies, intake data are self-reported (e.g., through 24-hour recalls of food intake, diet records, or food frequency questionnaires).

Potential sources of error in estimating intake from self-reported intake data include over- or underreporting of portion sizes and frequency of intake, omission of foods, and inaccuracies related to the use of food composition tables (IOM, 2000; Lichtman et al., 1992; Mertz et al., 1991). In addition, because a high percentage of the food consumed in the United States and Canada is not prepared from scratch in the home, errors can occur due to a lack of information on how a food was manufactured,

prepared, and served. Therefore, the values reported by nationwide surveys or studies that rely on self-reporting are often inaccurate and possibly biased, with a greater tendency to underestimate actual intake (IOM, 2000).

It is well known that energy intake is underreported in national surveys (Cook et al., 2000; Mertz et al., 1991; Schoeller et al., 1990). Estimates of underreporting of energy intake in the Third National Health and Nutrition Examination Survey were 18 percent of the adult men and 28 percent of the adult women participating (Briefel et al., 1997). Underreporters indicated that their fat intake was approximately 30.5 percent calories, whereas "adequate" reporters indicated a fat intake of 35 percent of calories. In addition, alcohol intake, which accounted for approximately 4 percent of the total energy intake in men and 2 percent in women, is thought to be routinely underreported as well (McDowell et al., 1994).

Adjusting for Day-to-Day Variation

Because of day-to-day variation in dietary intakes, the distribution of 1-day (or 2-day) intakes for a group is wider than the distribution of usual intakes, even though the mean of the intakes may be the same (for further elaboration, see Chapter 13). To reduce this problem, statistical adjustments have been developed (NRC, 1986; Nusser et al., 1996) that require at least 2 days of dietary data from a representative subsample of the population of interest. However, no accepted method is available to adjust for the underreporting of intake, which may average as much as 18 to 28 percent for energy (Briefel et al., 1997; Mertz et al., 1991).

DIETARY INTAKES IN THE UNITED STATES AND CANADA

Sources of Dietary Intake Data

The major sources of current dietary intake data for the U.S. population include the Third National Health and Nutrition Examination Survey (NHANES III), which was conducted from 1988 to 1994 by the U.S. Department of Health and Human Services, and the Continuing Survey of Food Intakes by Individuals (CSFII), which was conducted by the U.S. Department of Agriculture (USDA) from 1994 to 1996. NHANES III examined 30,000 individuals aged 2 months and older. A single 24-hour diet recall was collected for all participants. A second recall was collected for a 5 percent nonrandom subsample to allow adjustment of intake estimates for day-to-day variation. The CSFII collected two nonconsecutive 24-hour recalls from approximately 16,000 individuals of all ages. Both surveys used the food composition database developed by USDA to calculate nutrient

intakes (Perloff et al., 1990) and were adjusted by the method of Nusser and colleagues (1996).

Appendix D provides the mean and the 1st through 99th percentiles of intake for added sugars and amino acids from NHANES III, adjusted by methods described by the National Research Council (NRC, 1986) and by Feinleib and coworkers (1993) for persons aged 6 years and older. Appendix E provides similar data for energy, carbohydrate, dietary fiber, fat, fatty acids, cholesterol, protein, and alcohol by life stage group from the first phase of the CSFII, adjusted for day-to-day variation by the method of Nusser and colleagues (1996).

Survey data from 1990 to 1997 for several Canadian provinces are available for energy, carbohydrate, fat, saturated fat, and protein intake (Appendix F).

Food Sources

For some nutrients, two types of information are provided about food sources: identification of the foods that are the major contributors of the nutrients to diets in the United States, and the food sources that have the highest content of the nutrient. The determination of foods that are major contributors depends on both nutrient content of a food and the total consumption of the food (amount and frequency). Therefore, a food that has a relatively low concentration of a nutrient might still be a large contributor to total intake if that food is consumed in relatively large amounts.

SUMMARY

General methods for examining and interpreting the evidence for establishing reference intakes for macronutrients are presented in this chapter, with special attention given to infants, children, and pregnant and lactating women. Methodological problems and sources of dietary intake data are also discussed. Relevant details are provided in the nutrient chapters that follow.

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